Remarks

Claims 1-6, 9-12, and 14-21 are pending in this Application. Claims 1-6, 9-12, and 14-21 stand rejected on arguments laid out in the Office Action mailed December 7, 2007.

In the present Amendment, claims 1 and 9 have been amended such that they no longer recite "portions thereof, and combinations thereof."

A substitute Sequence Listing is being filed herewith that corrects inadvertent discrepancies in SEQ ID NO. 13 between the originally filed Sequence Listing and sequences disclosed in the specification as originally filed. The substitute Sequence Listing correctly lists the sequences as disclosed in the originally filed specificaition.

No new matter is added by these amendments.

Claim rejections – 35 USC § 112

Claims 1-6, 9-12, and 14-21 stand rejected under the first paragraph of 35 U.S.C. § 112 for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite chlorotoxin derivatives comprising certain sequences. In the Office Action mailed September 8, 2008, the Examiner sustained the argument that there are many different peptides within the genus claimed and that the specification is not enabling for so many different peptides. The Examiner argues, essentially, that because the claims included a recitation of "portions thereof, and combinations thereof," the number of peptides within the claimed genus is very high and that there is substantial variability in the genus.

In order to advance prosecution of the present case, Applicants have amended the claims such that they no longer recite "portions thereof, and combinations thereof." This substantially reduces the number of peptides encompassed by the claimed genus and the variability within the claimed genus. Applicants submit that the claims, as amended, are even more amply supported by the written description of the specification, as discussed further below.

Applicants maintain that 1) the relevant analysis is not related to the possible number of peptides encompassed by the claims but rather, whether those of ordinary skill in the art would recognize the inventor to have been in possession of the claimed invention at the time of filing; and 2) one of ordinary skill in the art would recognize that the inventors were in possession of the claimed invention at the time of filing.

The specification of the present application discloses a partial structure for, relevant identifying characteristics of, methods of making, and examples of chlorotoxin derivatives recited in the claims. Partial structures are defined in the claims according to listed sequences. Relevant identifying characteristics of the claim term "chlorotoxin derivative" are described in lines 25-32 of page 10 of the specification as originally filed. Methods of making such chlorotoxin derivatives are described in the paragraph beginning on page 10 and ending on page 11 of the specification as originally filed, and working examples of making and using such chlorotoxin derivatives are provided (see, *e.g.*, Examples 11-15, discussed below).

The Examiner asserted that "the claims lack written description because there is limited disclosure of a correlation between function and structure of the polypeptides *beyond those polypeptides specifically disclosed in the examples in the specification*." (emphases added). The Examiner seems to acknowledge that applicants have disclosed a correlation between structure and function using a number of polypeptides (which Applicants have specifically described in the specification), but appears dissatisfied with the extent of the disclosure, without providing specific reasons therefor.

Applicants submit that the present disclosure fully supports the claims. The present specification describes a slew of experiments elucidating the relationship between structure and function of chlorotoxin and chlorotoxin derivatives. For example, in Example 11 of the present specification, twenty-seven overlapping 10-mers derived from chlorotoxin were synthesized and tested for binding to prostate cancer cells. These experiments identified two core binding regions of chlorotoxin.

In Example 12, three 10-mer peptides (one each from the previously identified binding regions, and a negative control) were assayed in a crayfish paralysis assay, which is commonly used to determine the bio-activity of cholorotoxin. The results from these experiments strongly

implicated a particular region of chlorotoxin as being responsible for the paralyzing function of chlorotoxin. Applicants then tested six chlorotoxin derivatives containing the region (or a variant thereof) showing activity in the crayfish paralysis assay.

Applicants provided further disclosure of relationships between peptide structure and function in Example 13, which described the testing of nine different chlorotoxin-derived peptides for ability to bind glioma cells. From the results of such binding experiments, Applicants identified the contribution of certain residues to the cancer cell-binding function of chlorotoxin. Additional peptides were tested as described in Example 14, which summarized experiments with 9 alanine scan variants of a 9-mer peptide derived from chlorotoxin and identified as having binding activity to cancer cells. The experiments with the alanine scan variants provided further information correlating structure and function.

Even more experiments were conducted as described in Example 15 to further elucidate the relationship between structure and function of chlorotoxin and chlorotoxin derivatives. Example 15 describes results of experiments comparing cancer cell-binding activities of a chlorotoxin-derived peptides (one peptide from a binding domain and another from a non-binding domain) and homologous peptides derived from related toxins. Results from such binding assays, combined with sequence comparisons between the tested peptides, identified particular amino acid residues likely to play a role in binding to cancer cells. Applicants carried out further functional analyses (that is, analyses for ability to reduce proliferation of cancer cells) of a peptide that applicants had identified as having binding activity, as described in Example 15.

The binding motif whose sequence is listed as SEQ ID No. 13 embodies the many structure-function relationships elucidated from the above-summarized experiments. It is unclear what additional disclosure the Examiner deems necessary to describe the claimed invention.

The Examiner asserts that "the specification lacks sufficient descriptive support for the myriad of polypeptides embraced by the claims" and cites that "the description requirement of the patent statute requires a description of the invention, not an indication of a result that one might achieve if one made the invention." The Examiner also cited *In Re Kubin* and alleged that the present specification was similar to the specification in Kubin in failing to "adequately

describe what domains (and portions and combinations thereof) of the sequences are correlated with the required activity..." In contrast to the Examiner's allegation, Applicants have indeed described an invention, which encompasses the elucidation of domains and a motif within chlorotoxin involved in binding to cancer cells.

Nevertheless, in order to advance prosecution toward allowance, Applicants have amended the claims to substantially reduce the variety of polyeptides upon which the claims read. Applicants' removal of the terms "portions thereof, and combinations thereof" renders moot the Examiner's arguments in response to Applicant's arguments in the response filed June 9, 2008.

In light of the above remarks and amendments, this rejection should be withdrawn.

Claim rejections – 35 USC 102

Claims 1, 4-6, 9-12, and 19-20 remain rejected under 35 U.S.C. 102(e) as being anticipated by Samoylova *et al.* (US 2003/0216322) as evidenced by the Merck Manual entry for methotrexate. In laying out the grounds for this rejection, the Examiner argues that Samoylova teach peptides such as ELRGDSLP, which comprises a portion (RG) of chlorotoxin (SEQ ID NO.: 1 of the current invention), thus meeting the structural limitations of a portion of a chlorotoxin derivative as recited in claims 1, 9, and their dependents. The Examiner then remarks that "Samoylova teach compositions comprising a peptide and a chemotherapeutic agent."

In applying Samoylova *et al.* to this rejection, the Office Action relied on the premise that the peptide ELRGDSLP comprises a portion ('RG') of chlorotoxin. Applicants have amended the claims to remove recitation of "portions thereof and combinations thereof." Since the claims no longer recite "portions thereof," peptides taught by Samoylova *et al.* such as ELRGDSLP no longer meet the structural requirement of the recited polypeptides. Thus, the basis of this rejection has been rendered moot.

For all these reasons, this rejection should be withdrawn.

Claim rejections – 35 USC 103

Claims 1-6, 9-12, and 18-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Samoylova *et al.* (US 2003/0216322) and Stupp *et al.* (*The Lancet* v2 Sept 2001 552-560). Samoylova *et al.* teach phage-derived peptides for recognition and targeting of glial cell tumors. Stupp *et al.* teach administration of temozolomide for brain tumours and glioma.

In laying out the grounds for this rejection, the Examiner argues that "one would be motivated to substitute the chlorotoxin peptide for the phage-derived peptides particularly since Samoylova specifically teach glioma as a target and also since chlorotoxin is taught to have high-affinity specific binding to glioma cells."

The law holds, however, that a *prima facie* case of obviousness falls apart when the prior art teaches away from the claimed invention. In the present case, the very reference cited in the obviousness rejection *explicitly and strongly teaches away* from the claimed invention. The essential premise of the Samoylova *et al.* reference is that though some glioma-binding molecules were known in the art, additional molecules that could be used for targeting to glioma cells were needed.

Samoylova *et al.* mention chlorotoxin as one of the known molecules that have been used to target gliomas (see paragraph [0010]). Nevertheless, Samoylova *et al.* then disparage chlorotoxin and other known as a glioma-targeting agents by claiming that:

> "With the exception of the rearranged EGFRvIII and IL-4-independent IL-13Rα2 …, the surface molecules described above also are expressed by normal cells, limiting their usefulness in diagnosis or therapy. Additionally, there is frequently variation in marker expression within the same tumor mass over time with neoplastic progression or among the same type of tumors from different individuals. …*no single marker* will be able to provide diagnosis and/or targeting for all gliomas, but instead … an array of markers will be *necessary* for such purposes." (Emphases added; see paragraph [0012].)

The Examiner argues that it would be obvious to combine chlorotoxin (which Samoylova *et al.* disparage as being inadequate) or a chlorotoxin derivative (which Samoylova *et al.* do not teach at all) with a chemotherapeutic agent. Contrary to the Examiner's assertion, Samoylova *et al.* provide no motivation to do so. Samoylova *et al.* provide a variety of synthetic peptides, none of which are chlorotoxin derivatives. Samoylova *et al.* teach away from the claimed invention and at best provide a motivation for combining an array of entirely different peptides (which Samoylova *et al.* obtain from phage display experiments designed to discover previously unknown peptides, not by developing derivatives of chlorotoxin) with a chemotherapeutic agent.

Similarly, no motivation is provided by Stupp *et al.*, which teaches use of temozolomide for treatment of brain tumors. Stupp *et al.* do not teach or suggest use of chlorotoxin or chlorotoxin derivatives in combination with chemotherapeutic agents such as temozolomide. Instead, Stupp *et al.* suggest temozolomide as an adjuvant therapy after surgery, or in combination with radiotherapy or with nitrosureas, procarbazine, or irinotecan.

No combinaton of these two references could render obvious the claimed invention. Applicant respectfully requests removal of this rejection.

Double patenting

Claims 9-12 remain *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 13 of co-pending Application No. 10/522,810 in view of Stupp *et al.* (The Lancet v2 Sept 2001 552-560). Claim 1 remains *provisionally* rejected in the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 23 of co-pending Application No/ 11/731,661. Claims 1-6, 9-12, and 18-21 remain *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 23 of copending Application No. 11/731,661 in view of Samoylova *et a.* and Stupp *et al.* Claims 1, 4, and 9 remain *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4 and 21 of copending Application No. 11/547,875 in view of Stupp *et al.* Claims 1-6, 9-12, and

18-21 remain *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4 and 21 of copending Application No. 11/547,875 in view of Stupp *et al.* and Samoylova *et al.*

Applicants respectfully request that these provisional rejections be held in abeyance until the presently pending claims are deemed otherwise allowable. Applicants will address these provisional rejections upon indication of an allowance of the presently pending claims.

Conclusion

For all of these reasons, the rejections are not applicable to the claims and the claims should be allowed. A Notice to that effect is earnestly solicited.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account Number 03-1721. Applicant would like to thank the Examiner in advance for review of this request.

Respectfully submitted,

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